Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS)

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Hypothesis The principle aim of the current study is to test the hypothesis that the long-term use of highly purified EPA (eicosapentaenoic acid: 1800 mg/day), in addition to HMG-CoA reductase inhibitor, is effective in preventing cardiovascular events in Japanese patients with hypercholesterolemia.

Background Epidemiological and clinical evidence suggest that intake of long-chain polyunsaturated n-3 fatty acids (PUFAs), which are abundant in fish, might have a significant role in the prevention of coronary artery disease, as marine PUFAs have multiple biological functions through lipid-dependent and lipid-independent mechanisms.

Methods The Japan EPA Lipid Intervention Study (JELIS) is a prospective, randomized, open-label, blinded end point trial including both primary and secondary prevention strata, with a maximum follow-up of 5 years. Its main purpose is to examine the clinical effectiveness of EPA oil given as an additional treatment to patients taking HMG-CoA reductase inhibitors for hypercholesterolemia. A primary end point is major coronary events: sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or coronary artery bypass grafting. Secondary end points include all-cause mortality, stroke, peripheral artery disease, and cancer. Baseline study composition comprises 15,000 participants (4204 men and 10,796 women) in the primary prevention stratum and 3645 (1656 men and 1989 women) in the secondary stratum. The minimum age is 40 years for men, women are required to be postmenopausal, and all patients must be ≤75 years of age. The mean age of participants is 61 years, and 69% are female. The schedule for plasma fatty acid composition measurement is as follows: at baseline, at 6 month, and yearly thereafter. The mean baseline total and low-density lipoprotein cholesterol levels were 275 mg/dL (7.1 mmol/L) and 180 mg/dL (4.6 mmol/L).

Results Results are expected in 2005.

Conclusion JELIS is a large clinical trial that will evaluate whether EPA can make an additional improvement in mortality and morbidity of coronary artery disease beyond that of HMG-CoA reductase inhibitor treatment. (Am Heart J 2003;146:613–20.)

Beginning with the study by Dyerberg et al on Greenland Eskimos in the late 1970s,[1] epidemiological studies from many countries including Finland, Italy, Japan, and The Netherlands have suggested that an increased intake of dietary fish or fish oil rich in the long-chain polyunsaturated n-3 fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is inversely related to the risk of atherothrombotic diseases, in particular coronary artery disease (CAD).[2–4]

Results of many prospective observational cohort studies have found that diets rich in marine PUFAs may be protective against major cardiovascular events, including mortality from CAD, total cardiovascular death, all-cause mortality, and nonfatal myocardial infarction.

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Thus, 2 randomized, controlled, secondary prevention trials were performed to examine the effects of dietary fish on the risk of death from CAD in patients after myocardial infarction. The Diet and Reinfarction Trial (DART) reported that patients who were advised to increase their dietary intake of fish to at least 2 fish meals per week had a 29% decrease in all-cause mortality over 2 years.[5] The GISSI-Prevenzione trial showed that there was a 20% decrease in all death, a 30% decrease in cardiovascular deaths, and a 45% decrease in sudden deaths associated with a daily supplement of n-3 PUFAs (1g daily, EPA/DHA = 1:2) in patients with recent myocardial infarction.[6] These trial results are concordant with a body of epidemiological data. It has not yet been proved by clinical trials of primary prevention that marine n-3 PUFAs reduce the mortality and morbidity of CAD in high-risk subjects. Most trials have involved the use of diets supplemented by intake of fish, fish oils, or capsules containing fish oil extracts. These may contain a number of other fatty acids and different components. Thus, an evaluation of the specific effects of each n-3 PUFA was not possible. To date, only a few studies have examined the effects of purified n-3 PUFA preparations in human subjects for short observation periods.

Although the underlying mechanisms of protective action of n-3 PUFAs against CAD remain to be established, their multiple cardiovascular effects have received much attention. The potential mechanisms are lower levels of serum lipids,[7–9] antithrombotic properties and relaxation in coronary arteries,[10–14] anti-inflammatory properties,[15–18] anti-platelet–derived growth factor properties,[19] natural ligands for peroxisome proliferator activated receptors,[20,21] and antiarrhythmic properties.[22]

Rationale for the JELIS

It is well established that cholesterol lowering with hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors conveys potential for primary and secondary prevention of cardiovascular events in hypercholesterolemic patients.[23–26] Preliminary data on pravastatin combined with fish oil have shown several beneficial effects on the lipid profile of patients with a mixed type of hyperlipidemia.[27–29] This combination therapy effectively reduced the concentration of low-density lipoprotein as well as that of total cholesterol. It was also remarkably safe during short-term use and expected to be clinically beneficial.

However, no clinical intervention trial data have been collected to determine whether the addition of EPA to conventional therapy with an HMG-CoA reductase inhibitor is effective in preventing cardiovascular events.

This study is designed to test the fundamental hypothesis that treatment with highly purified EPA ethyl ester together with lipid lowering with an HMG-CoA reductase inhibitor is more effective than treatment without EPA in reducing major coronary events. Such coronary events involve CAD deaths including sudden cardiac death, fatal and nonfatal myocardial infarction, and unstable angina pectoris. Other objectives are to evaluate the effect of EPA on the frequency of stroke and all-cause death, the long-term safety of EPA, and the relationship between plasma fatty acid levels and the onset of cardiovascular events.

Methods

Study design

The JELIS is a prospective, randomized, open-label, blinded-end point clinical trial designed to examine the clinical efficacy of EPA oil administered as an adjuvant agent to patients under treatment with HMG-CoA reductase inhibitors for hypercholesterolemia. Participants are randomly assigned to either EPA adjuvant treatment or none in an open fashion (ie, an unblinded manner). Because all patients receive reductase inhibitors, we cannot assess whether the inhibitors and EPA work synergistically.

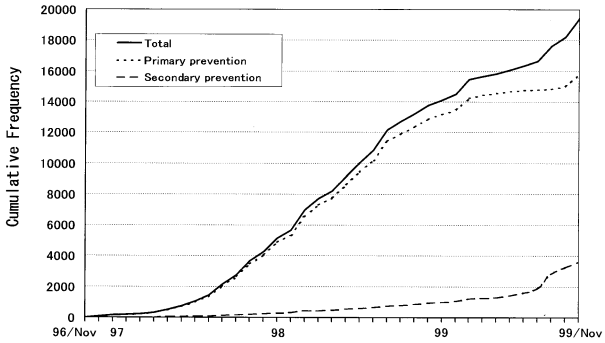
The primary prevention stratum was defined as participants who had (1) no history of myocardial infarction (MI) or angina pectoris and with neither angioplasty/stenting nor coronary artery bypass graft (CABG) until randomization, and (2) no clinical manifestations of angina pectoris or electrocardiograph (ECG) abnormalities at randomization. The secondary prevention stratum was defined as those who had (1) history of well-documented MI or angina pectoris with neither angioplasty/stenting nor CABG until randomization, and/or (2) stable, controlled angina pectoris at randomization.

In the primary and secondary prevention strata, a primary end point is major coronary events, which include sudden cardiac death, fatal and nonfatal MI, unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or CABG. Secondary end points are all-cause mortality, mortality and morbidity of CAD, stroke, peripheral artery disease (arteriosclerosis obliterans [ASO]), and cancer. Clinical end points are ascertained once a year by the Endpoints Adjudication Committee: expert cardiologists and neurologists who are blinded to the assigned groups. However, the assessment of the end points is performed without breaking a key code, by a blinded-end point approach. Each participant is followed-up for a maximum of 5 years.

Random allocation

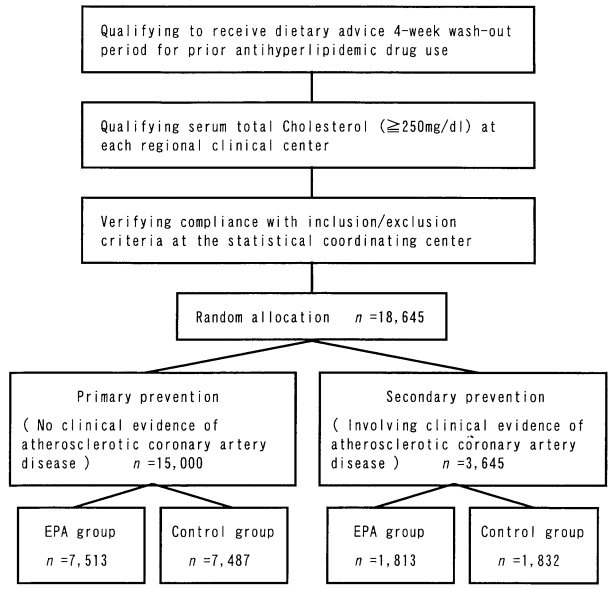
This study used a statistical coordinating center, Toyama Medical and Pharmaceutical University, to manage patient registration, which included the confirmation of eligibility criteria, operation of the randomization scheme, and data management. We used a permuted block randomization with a block size of 4. Multiple blocks were assigned according to the number of participants enrolled at each center. Stratification was based on the prevention stratum (primary or sec-

Figure 1



Monthly chart of the recruitment process.

Figure 2



Trial profile.

ondary). The results of the randomization scheme were concealed to the investigators and participants.

Patient population

Between November 1996 and November 1999, we enrolled a total of 19,466 participants with hypercholesterolemia from all regions of Japan; a total of 821 cases were excluded as ineligible.

The intention-to-treat data set currently involves 18,645 participants, with 15,000 (80%) for primary and 3645 (20%) for secondary prevention who were randomly assigned to EPA plus HMG-CoA reductase inhibitors or HMG-CoA reductase inhibitors only.

The monthly increase of the enrollment is shown in Figure 1, and Figure 2 illustrates the trial profile.

The study patients were recruited by local physicians participating in this study with the help of regional organizing committees. Eligible participants had a total cholesterol level of ≥250 mg/dL (6.5 mmol/L), which corresponds to an LDL cholesterol level of 170 mg/dL (4.4 mmol/L), at baseline. The minimum age was 40 years for men; women were required to be postmenopausal. Maximum patient age was 75 years (due to the 5-years follow-up). Informed written consent was obtained from each patient. All participants are Japanese for the simple reason that highly purified EPA is allowed as treatment for hyperlipidemia in Japan. Inclusion and exclusion criteria are listed in Table I.

Local physicians monitor dietary and medication compliance at every clinical visit.

The schedule of observations is shown in Table II.

Baseline data

Patients were divided into the EPA group (n = 9326) or control group (n = 9319).

The baseline demographic and clinical characteristics of JELIS are shown in Table III.

In the primary prevention stratum (n = 15,000), the mean age was 56 years for men (28%) and 62 years for women (72%). Prevalence of smoking and drinking were 17% and 24%, respectively. Concomitant diseases were prevalent in approximately 47% of the participants in the order of hypertension, diabetes, stroke, hepatic disease, and renal disease. ECG abnormalities were present in 17%. The mean total cholesterol level was 277 mg/dL at baseline with the standard deviation of 28 mg/dL. Mean LDL and high-density lipoprotein (HDL) cholesterol levels were 181 mg/dL and 59 mg/dL, respectively. There was no evidence of high blood pressure on average.

In the secondary prevention stratum (n=3645), the mean age was 62 years for men (45%) and 65 years for women (55%). Prevalence of smoking and drinking were 25% and 30%, respectively. Prior myocardial infarction was present in 28% and stable angina was reported in 79%. Concomitant diseases were found in approximately 58% of the participants, in the order of hypertension, diabetes, stroke, hepatic disease, and renal disease. ECG abnormalities were present in 58%. Mean total cholesterol level was 270 mg/dL at baseline with a standard deviation of 28 mg/dL. Mean LDL and HDL cholesterol were 177 mg/dL and 55 mg/dL, respectively.

Figure 3 shows the plasma fatty acids composition at baseline. C18:2 omega 6 (linoleic acid), C16:0 (palmitic acid) and C18:1 omega 9 (oleic acid) were the dominant fatty acids. C18:0 (stearic acid), C20:4 omega 6 (arachidonic acid), C22:6 omega 3 (docosahexaenoic acid), and C20:5 omega 3 (eicosapentaenoic acid) followed, but no statistically significant differences were observed in the prevention stratum.

Treatment/preparations

EPA is administered at a dose of 600 mg, three times a day after meals (total 1800 mg/day). We use EPADEL Capsule 300TM (Mochida Pharmaceutical Co, Ltd, Tokyo, Japan) con-

Table I. Inclusion and exclusion criteria

Inclusion criteria
- Hyperlipidemic patients with serum total cholesterol of 250 mg/dL or more
  - (Measurement of serum total cholesterol)
    - Serum total cholesterol should be measured twice at interval of 2–4 weeks. A single measurement is acceptable if the cholesterol is measured by blood collection at fasting under strict compliance with dietary advice after withdrawal of the antihyperlipemic drug.
  - (Wash Out)
    - The wash out period of 4 weeks (8 weeks for probucol) is necessary in patients under treatment with antihyperlipemic drug. However, if treatment with the antihyperlipemic drug was started within 6 months of the initiation of the study, the patient can participate in the study without the washout period.
- Men aged 40–75 years or women after menopause to 75 years
- Patients who have already received appropriate dietary advice

Exclusion criteria
- Acute myocardial infarction occurring within last 6 months
- Unstable angina pectoris
- A history or complication of serious heart disease (severe arrhythmia, heart failure, cardiac myopathy, valvular disease, congenital disease, etc.)
- Receiving cardiovascular reconstruction within last 6 months
- Cerebrovascular disorders occurring within last 6 months
- Complication of serious hepatic disease or renal disease
- Malignant tumor
- Uncontrollable diabetes
- Hyperlipidemia arising from the following diseases:
  - Nephrotic syndrome, hypothyroidism, Cushing's syndrome, secondary hyperlipidemia due to other disease
- Hyperlipidemia due to some drugs such as steroid hormone
- Hemorrage (hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, vitreous hemorrhage, etc.)
- Hemorrhagic diathesis
- Hypersensitivity to the study drug fomulation
- Patients intending to undergo surgery
- Patients judged to be inappropriate by the physician in charge

Table II. Schedule of the observations during the study period

	Pretreatment period		Treatment period (months)											
	−8	−4	0	2	6	12	18	24	30	36	42	48	54	60
Dietary advice			x			x		x		x		x		x
Compliance check			x			x		x		x		x		x
Smoking and drinking			x			x		x		x		x		x
Vital signs (including ECG)			x			x		x		x		x		x
Adverse and clinical events			←											→
Serum lipids (at each clinical center)	x	x	x		x	x		x		x		x		x
Fatty acids (central laboratory)			x		x	x		x		x		x		x
Clinical visits	x	x	x	x	x	x	x	x	x	x	x	x	x	x

taining 300 mg of highly (>98%) purified EPA ethyl ester (ethyl all-cis-5,8,11,14,17-icosapentaenoate) per capsule. EPA is actually purified from a long-chain polyunsaturated fatty acid present in fish oil (Figure 4). EPADEL Capsule 300 was launched in the Japanese market in 1990 for the treatment of ASO and hyperlipidemia. The usual adult dose is 600 mg of ethyl icosapentaenoate: 2 capsules administered orally 3 times daily immediately after meals.

Concomitant treatment

Either pravastatin or simvastatin was prescribed for all participants as a first-line therapy, these being the 2 HMG-CoA reductase inhibitors available in Japan at the initiation of this study.

Dosage, as recommended by Ministry of Health, Labour and Welfare (MHLW), is as follows: pravastatin 10 mg, once a day or simvastatin 5 mg, once a day. With serious hypercholesterolemia, defined as a serum cholesterol level not controlled by the recommended dosage, these can be increased to 20 mg and 10 mg, respectively.

No treatment with other antihyperlipidemic agents was allowed during the study period. However, other kinds of medications were taken as needed. This regime will be followed for a maximum of 5 years.

Table III. Baseline characteristics of primary and secondary prevention strata

	Primary prevention stratum		Secondary prevention stratum	
	EPA group (n = 7513)	**Control group (n = 7487)**	**EPA group (n = 1813)**	**Control group (n = 1832)**
Age (y)				
≤49 (%)	884 (11.8)	906 (12.1)	114 (6.3)	128 (7.0)
50–59 (%)	2481 (33.0)	2549 (34.0)	413 (22.8)	435 (23.7)
60–69 (%)	2976 (39.6)	2913 (38.9)	806 (44.5)	777 (42.4)
≥70 (%)	1172 (15.6)	1119 (14.9)	480 (26.5)	492 (26.9)
Male	56 ± 10	56 ± 10	62 ± 9	61 ± 9
Female	62 ± 7	62 ± 7	65 ± 7	65 ± 7
Sex (%)				
Male	2113 (28.1)	2091 (27.9)	838 (46.2)	818 (44.7)
Female	5400 (71.9)	5396 (72.1)	975 (53.8)	1014 (55.3)
Smoking (%)	1323 (17.6)	1244 (16.6)	485 (26.8)	435 (23.7)
Drinking (%)	1837 (24.5)	1830 (24.4)	540 (29.8)	542 (29.6)
BMI (kg/m^2)	24.0 ± 3.6	23.9 ± 3.5	24.0 ± 3.9	24.1 ± 4.0
ECG abnormality at resting (%)	1299 (17.3)	1245 (16.6)	1046 (57.7)	1067 (58.2)
CAD (%)				
Angina				
Effort	–	–	1018 (56.2)	1076 (58.7)
Spontaneous	–	–	389 (21.5)	392 (21.4)
Myocardial infarction	–	–	539 (29.7)	495 (27.0)
Angioplasty				
PTCA	–	–	363 (20.0)	328 (17.9)
Coronary bypass	–	–	114 (6.3)	110 (6.0)
Endovascular stent	–	–	130 (7.2)	120 (6.6)
DCA	–	–	9 (0.5)	9 (0.5)
PTCR	–	–	22 (1.2)	18 (1.0)
Others	–	–	11 (0.6)	7 (0.4)
Other complications (%)				
Diabetes	1101 (14.7)	1086 (14.5)	400 (22.1)	414 (22.6)
Hypertension	2521 (33.6)	2451 (32.7)	781 (43.1)	802 (43.8)
Stroke	370 (4.9)	320 (4.3)	108 (6.0)	131 (7.2)
Hepatic diseases	314 (4.2)	304 (4.1)	61 (3.4)	57 (3.1)
Renal diseases	177 (2.4)	181 (2.4)	59 (3.3)	67 (3.7)
Total cholesterol (mg/dL)	276.6 ± 28.0	276.9 ± 27.8	270.0 ± 27.7	270.1 ± 29.0
LDL cholesterol (mg/dL)	180.5 ± 34.5	181.4 ± 33.7	177.1 ± 32.2	176.3 ± 32.9
HDL cholesterol (mg/dL)	59.4 ± 17.7	59.0 ± 18.1	55.4 ± 19.2	55.5 ± 19.6
Triglyceride (mg/dL)	187.9 ± 147.8	189.2 ± 159.5	189.8 ± 127.1	198.6 ± 151.9
Systolic blood pressure (mm Hg)	135.6 ± 18.7	135.5 ± 18.2	137.0 ± 18.0	137.1 ± 18.3
Diastolic blood pressure (mm Hg)	79.7 ± 11.0	79.9 ± 11.1	78.7 ± 10.9	79.3 ± 11.0

Plus-minus values are means ± SD.

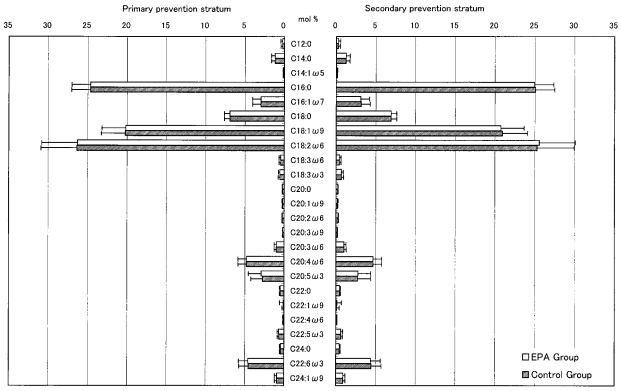
Calculations and analysis

For the primary prevention stratum, CAD morbidity and mortality in the Japanese general population was estimated at 5.3 per 1000 person years.[30] Because the JELIS population is restricted to those with a total cholesterol level of ≥250 mg/dL, we estimated a 10% higher risk for our cohort: 5.8 per 1000 person years. For the secondary prevention stratum, CAD morbidity and mortality was reported at 57.6 per 1000 person years[23] from Scandinavian countries, where people are considered to be at an extremely high risk for CAD compared to Japan. The incidence of CAD in the secondary prevention stratum was estimated as 21.3 per 1000 person years.

In fact, for primary prevention the incidence was 5.8 per 1000 person years in Japan,[30] whereas it was 15.8 per 1000 person years in Scotland.[24] Thus, the ratio of these rates, 2.7 (15.8 divided by 5.8), was used for adjustment. We also assumed that the proportion of participants in the primary prevention stratum would be 65%.

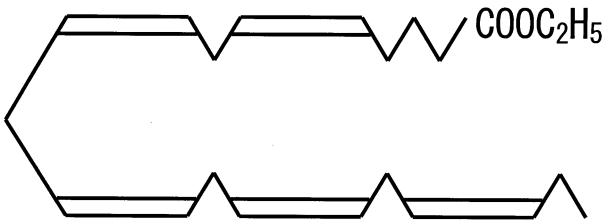
With respect to risk reduction, several megatrials and meta-analyses involving HMG-CoA reductase inhibitors[31] have estimated an approximate 30% reduction of CAD morbidity and mortality compared to none or placebo. Given the DART and GISSI results, we optimistically supposed that EPA would further reduce the risk by 25%, conditional on the use of HMG-CoA reductase inhibitors. Therefore, comedication of EPA with HMG-CoA reductase inhibitors should reduce the risk by 47.5% compared to no treatment.

Figure 3



Fatty acids composition at baseline.

Figure 4



Chemical structure of EPA ethyl ester.

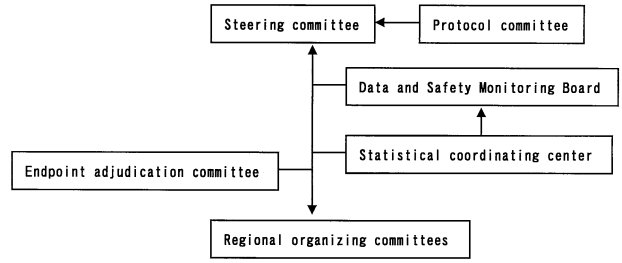
Assuming we perform the log-rank test with 2-sided significance, 12,600 participants are required to achieve a minimum statistical power of 80%. The accrual period is assumed to be 3 years with a follow-up period of 5 years at the most.

As more participants than expected were recruited in the primary prevention stratum (80%), sample size projection correction increased the number of participants required from 12,600 to 18,000.

All analyses follow an intention-to-treat approach. Analyses of time-to-event data are performed using the Kaplan-Meier method and the log-rank test is performed to test treatment group differences. The relative risk and its 95% CI are calculated from the Cox proportional hazard model. Adverse events are compared between groups using the Fisher exact test. The analysis is performed according to the stratum of either primary or secondary prevention. Statistical significance is set at the $<5\%$ level with a 2-sided test.

Formal interim analysis is to be performed twice during the trial. The first will be 2 years after the final enrollment of participants (ie, in early 2002). The second will be mid 2004. The final analysis is expected in late 2005. The interim analysis will apply the Lan-DeMets boundary based on the number of cardiovascular events, supported by computing a conditional power to demonstrate the superiority of EPA against the control group, toward the end of the trial.

Figure 5



Organization of JELIS.

Trial organizational structure

The organizational structure of JELIS is illustrated in Figure 5. This study is conducted under the scientific direction of the Steering Committee. The External Data and Safety Monitoring Board is responsible for identifying safety issues and interpreting emerging study data.

Discussion

The preventive effect of n-3 PUFAs for CAD morbidity and mortality has been reported in various epidemiological researches and cohort studies.[32–34] JELIS is the first large-scale, randomized, controlled trial of highly purified EPA in hypercholesterolemia, including both primary and secondary prevention strata and using EPA as an adjuvant treatment with an HMG-CoA reductase inhibitor as the baseline drug. Study patients are expected to demonstrate that cardiovascular events can be further decreased by 25% beyond that expected by the use of HMG-CoA reductase inhibitors alone.

Several large-scale clinical studies have evaluated the effects of HMG-CoA reductase inhibitors in hypercholesterolemia.[23–26] Comparing our study with 4S,[23] WOS,[24] CARE,[25] LIPID,[26] and the currently ongoing MEGA STUDY[34] in Japan, the number of participants enrolled for JELIS surpasses that recorded for all the others. Subgroup analyses by age, sex, and concomitant disease might also produce important information on differences in event rates between Japan and other countries.

Although the inhibitory effect of dietary n-3 PUFAs on cardiovascular events has been assessed in a few case-control studies and in 2 secondary prevention trials, there has been no report on clinical outcomes assessed in randomized controlled trials involving primary prevention cases. JELIS is the first attempt to collect such data.

With respect to secondary prevention cases, randomized controlled trials such as DART[5] and GISSI[6] showed an inhibitory effect of n-3 PUFAs on cardiovas-

cular events. These studies, which advised consumption of meals containing fish or EPA plus DHA preparations, had shorter follow-up periods than JELIS, which has a median duration of 2 years to date, with a range of 1 to 4 years.

Further, because JELIS measured the plasma fatty acid fraction once a year, it is possible to study the relationship between changes in the composition of blood fatty acids, such as EPA, as well as oleic acid and linoleic acid, and the onset of cardiovascular events.

There have been relatively recent discussions on the appropriateness of prescribing cholesterol-lowering drugs to postmenopausal women.[35] Cholesterol-lowering drugs are taken by many Japanese women. The subclass analysis of our study may address the usefulness of these drugs for women.

As noted, we are conducting this trial on an exclusively Japanese population mainly because EPA is an allowed treatment for hyperlipidemia in Japan. Should our fundamental hypothesis be proven, it will then need to be argued whether the results can be extrapolated to non-Japanese populations and whether EPA is differentially effective between populations.

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